2. (Amended) An isolated nucleic acid comprising a nucleotide sequence encoding a protein selected from the group consisting of an hcAMP-GEFII protein having the amino acid sequence of SEQ ID NO: 18, a normal variant of said hcAMP-GEFII protein, and a mutant of said hcAMP-GEFII protein.

4. (Amended) An isolated nucleic acid as in claim 2 wherein said nucleic acid encodes a normal variant of said hcAMP-GEFII protein and wherein said nucleotide sequence comprises a sequence encoding a normal variant of said hcAMP-GEFII protein and capable of hybridizing under stringent hybridization conditions to a sequence complementary to a sequence encoding a protein comprising the human cAMP-GEFII amino acid sequence of SEQ ID NO: 18.

5. (Amended) An isolated nucleic acid comprising a nucleotide sequence of at least 8 consecutive nucleotides selected from the group consisting of (a) nucleotides 1-2600 of SEQ ID NO. 17, and (b) a sequence complementary to nucleotides 1-2600 of SEQ ID NO. 17.

6. (Amended) An isolated nucleic acid comprising a nucleotide sequence of at least 10 consecutive nucleotides selected from the group consisting of (a) nucleotides 1-2602 of SEQ ID NO. 17, and (b) a sequence complementary to nucleotides 1-2602 of SEQ ID NO: 17.

7. (Amended) An isolated nucleic acid comprising a nucleotide sequence of at least 15 consecutive nucleotides selected from the group consisting of (a) nucleotides 1-2607 of SEQ ID NO. 17, and (b) a sequence complementary to nucleotides 1-2607 of SEQ ID NO. 17 .

9. (Amended) An isolated nucleic acid comprising a nucleotide sequence encoding at least one functional domain of an hcAMP-GEFII protein having the amino acid sequence of SEQ ID NO. 18; a normal variant of said hcAMP-GEFII protein, or a mutant of said hcAMP-GEFII protein.

11. (Amended) An isolated nucleic acid comprising a nucleotide sequence encoding an antigenic determinant of an hcAMP-GEFII protein (SEQ ID NO: 18) and selected from the group consisting of a normal variant of said hcAMP-GEFII protein, and a mutant of said hcAMP-GEFII protein.

38. (Amended) An isolated nucleic acid comprising a variant nucleotide sequence of a human cAMP-GEFII gene (SEQ ID NO: 17), said variant being selected from the group consisting of an allelic variant of said human cAMP-GEF II gene, and a heterospecific homologue of said human cAMP-GEFII gene.

39. (Amended) An isolated nucleic acid encoding a variant amino acid sequence of a human cAMP-GEFII protein (SEQ ID NO: 18), said variant being selected from the group consisting of an allelic variant of said human cAMP-GEF II protein, and a heterospecific homologue of said human cAMP-GEFII protein.

40. (Amended) An isolated nucleic acid comprising a recombinant vector including a nucleotide sequence selected from the group consisting of SEQ ID NO: 17, and a sequence complementary to SEQ ID NO: 17.

45. (Amended) An isolated nucleic acid as in claim 41 wherein said expression vector encodes at least a functional domain of a protein selected from the group consisting of an hcAMP-GEFII protein having the amino acid sequence of SEQ ID NO: 18, a normal variant of said hcAMP-GEFII, and a mutant of said hcAMP-GEFII.

48. (Amended) An isolated nucleic acid comprising a recombinant expression vector including nucleotide sequences corresponding to an endogenous regulatory region of an hcAMP-GEFII gene (SEQ ID NO. 17).

B8 50. (Amended) A host cell comprising an expression vector of any one of claims 41-49, or a descendant thereof, wherein said host cell is transformed *in vitro* with said expression vector.

B9 and D3 62. (Amended) A method for producing at least a functional domain of an hcAMP-GEFII protein (SEQ ID NO: 18), said method comprising culturing a host cell of any of claims 50-54 under suitable conditions to produce said protein by expressing said nucleic acid.

B10 118. (Amended) A composition comprising an expression vector operably encoding an hcAMP-GEFII protein (SEQ ID NO: 18) or a normal variant thereof, wherein said expression vector may express said hcAMP-GEFII protein or normal variant in a human subject, and a pharmaceutically acceptable carrier.

B11 120. (Amended) A composition comprising an expression vector operably encoding an antisense sequence of an hcAMP-GEFII gene (SEQ ID NO: 17), wherein said expression vector may express said antisense sequence in a human subject, and a pharmaceutically acceptable carrier.

Basis for Amendments

Claims 1, 3, 8, 10, and 119 have been cancelled without prejudice and without the intention of abandoning the subject matter claimed therein. Indeed, Applicants may choose to pursue claims of the same scope, or narrower or broader scope, in the form of one or more related applications at a later date.

Claims 2, 4-7, 9, 11, 38, 39, 40, 45, 62, 118, and 120 have been amended to delete subject matter drawn to a non-elected invention, and to include reference to sequence identifier numbers. Claims 5-7 have also been amended to recite specific nucleotides of the sequence of SEQ ID NO: 17. Claims 38, 39, 50, 118, and 120 have been further amended for clarity. Claims 38 and 39 have been further amended to recite a "variant"

CLAIMS

What is claimed is:

1. An isolated nucleic acid comprising a nucleotide sequence encoding a protein selected from the group consisting of a normal CalDAG-GEFI protein, a mutant CalDAG-GEFI protein, a normal CalDAG-GEFII protein, and a mutant CalDAG-GEFII protein.

2. An isolated nucleic acid comprising a nucleotide sequence encoding a protein selected from the group consisting of a normal cAMP-GEFI protein, a mutant cAMP-GEFI protein, a normal cAMP-GEFII protein, and a mutant cAMP-GEFII protein.

3. An isolated nucleic acid as in claim 1 wherein said nucleic acid encodes a normal CalDAG-GEF protein and wherein said nucleotide sequence is selected from the group consisting of

(a) a sequence encoding a protein comprising the human CalDAG-GEFI amino acid sequence of SEQ ID NO: 4;

(b) a sequence encoding a protein comprising the murine CalDAG-GEFI amino acid sequence of SEQ ID NO: 2;

(c) a sequence encoding a protein comprising the human CalDAG-GEFII amino acid sequence of SEQ ID NO: 8; and

(d) a sequence encoding a protein comprising the murine CalDAG-GEFII amino acid sequence of SEQ ID NO: 6; and

(e) a sequence encoding a normal CalDAG-GEF protein and capable of hybridizing to a sequence complementary to any sequence of (a) - (d) under stringent hybridization conditions.

4. An isolated nucleic acid as in claim 2 wherein said nucleic acid encodes a normal cAMP-GEF protein and wherein said nucleotide sequence is selected from the group consisting of

(a) a sequence encoding a protein comprising the human cAMP-GEFI amino acid sequence of SEQ ID NO: 12;

(b) a sequence encoding a protein comprising the alternatively spliced human cAMP-GEFI amino acid sequence of SEQ ID NO: 14;

(c) a sequence encoding a protein comprising the rat cAMP-GEFI amino acid sequence of SEQ ID NO: 10;

(d) a sequence encoding a protein comprising the human cAMP-GEFII amino acid sequence of SEQ ID NO: 18;

(e) a sequence encoding a protein comprising the rat cAMP-GEFII amino acid sequence of SEQ ID NO: 16; and

(f) a sequence encoding a normal cAMP-GEF protein and capable of hybridizing to a sequence complementary to any sequence of (a) - (e) under stringent hybridization conditions.

5. An isolated nucleic acid comprising a nucleotide sequence of at least 8 consecutive nucleotides selected from the group consisting SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO. 17, and a sequence complementary to any of these sequences.

6. An isolated nucleic acid comprising a nucleotide sequence of at least 10 consecutive nucleotides selected from the group consisting SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO. 17, and a sequence complementary to any of these sequences.

7. An isolated nucleic acid comprising a nucleotide sequence of at least 15 consecutive nucleotides selected from the group consisting SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO. 17, and a sequence complementary to any of these sequences.

8. An isolated nucleic acid comprising a nucleotide sequence encoding at least one functional domain of a CalDAG-GEF protein selected from the group consisting of a normal CalDAG-GEFI protein, a mutant CalDAG-GEFI protein, a normal CalDAG-GEFII protein, and a mutant CalDAG-GEFII protein.

9. An isolated nucleic acid comprising a nucleotide sequence encoding at least one functional domain of a cAMP-GEF protein selected from the group consisting of a normal cAMP-GEFI protein, a normal cAMP-GEFII protein, a mutant cAMP-GEFI protein, and a mutant cAMP-GEFII protein.

10. An isolated nucleic acid comprising a nucleotide sequence encoding an antigenic determinant of a CalDAG-GEF protein selected from the group consisting of a normal CalDAG-GEFI protein, a normal CalDAG-GEFII protein, a mutant CalDAG-GEFI protein, and a mutant CalDAG-GEFII protein.

11. An isolated nucleic acid comprising a nucleotide sequence encoding an antigenic determinant of a cAMP-GEF protein selected from the group consisting of a normal cAMP-GEFI protein, a normal cAMP-GEFII protein, a mutant cAMP-GEFI protein, and a mutant cAMP-GEFII protein.

12. A method for identifying an allelic variant or heterospecific homologue of a human CalDAG-GEF gene comprising:

choosing a nucleic acid probe or primer capable of hybridizing to a human CalDAG-GEF gene sequence under stringent hybridization conditions;

mixing said probe or primer with a sample of nucleic acids which may contain a nucleic acid corresponding to said variant or homologue; and

detecting hybridization of said probe or primer to said nucleic acid corresponding to said variant or homologue.

13. A method as in claim 12 wherein said human CalDAG-GEF gene sequence is selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 7.

14. A method as in claim 12 wherein said sample comprises a sample of nucleic acids selected from the group consisting of human genomic DNA, human mRNA, and human cDNA.

15. A method as in claim 12 wherein said sample comprises a sample of nucleic acids selected from the group consisting of mammalian genomic DNA, mammalian mRNA, and mammalian cDNA.

16. A method as in claim 12 wherein said sample comprises a sample of nucleic acids selected from the group consisting of invertebrate genomic DNA, invertebrate mRNA, and invertebrate cDNA.

17. A method as in claim 12 further comprising the step of isolating said nucleic acid corresponding to said variant or homologue.

18. A method as in claim 12 wherein said nucleic acid is identified by hybridization.

19. A method as in claim 12 wherein said nucleic acid is identified by PCR amplification.

20. A method for identifying allelic variants or heterospecific homologues of a human cAMP-GEF gene comprising:

choosing a nucleic acid probe or primer capable of hybridizing to a human cAMP-GEF gene sequence under stringent hybridization conditions;

mixing said probe or primer with a sample of nucleic acids which may contain a nucleic acid corresponding to said variant or homologue; and

detecting hybridization of said probe or primer to said nucleic acid corresponding to said variant or homologue.

21. A method as in claim 12 wherein said human cAMP-GEF gene sequence is selected from the group consisting of SEQ ID NO: 11, SEQ ID NO: 13, and SEQ ID NO: 17.

22. A method as in claim 20 wherein said sample comprises a sample of nucleic acids selected from the group consisting of human genomic DNA, human mRNA, and human cDNA.

23. A method as in claim 20 wherein said sample comprises a sample of nucleic acids selected from the group consisting of mammalian genomic DNA, mammalian mRNA, and mammalian cDNA.

24. A method as in claim 20 wherein said sample comprises a sample of nucleic acids selected from the group consisting of invertebrate genomic DNA, invertebrate mRNA, and invertebrate cDNA.

25. A method as in claim 20 further comprising the step of isolating said nucleic acid corresponding to said variant or homologue.

26. A method as in claim 20 wherein said nucleic acid is identified by hybridization.

27. A method as in claim 20 wherein said nucleic acid is identified by PCR amplification.

28. A method for identifying an allelic variant or heterospecific homologue of a human CalDAG-GEF gene comprising:

choosing an antibody capable of selectively binding to a human CalDAG-GEF protein;

mixing said antibody with a sample of proteins which may contain a protein corresponding to said variant or homologue; and

detecting binding of said antibody to said protein corresponding to said variant or homologue.

29. A method as in claim 28 wherein said sample comprises a sample of proteins selected from the group consisting of human proteins, human fusion proteins, and proteolytic fragments thereof.

30. A method as in claim 28 wherein said sample comprises a sample of nucleic acids selected from the group consisting of mammalian proteins, mammalian fusion proteins, and proteolytic fragments thereof.

31. A method as in claim 28 wherein said sample comprises a sample of nucleic acids selected from the group consisting of invertebrate proteins, invertebrate fusion proteins, and proteolytic fragments thereof.

32. A method as in claim 28 further comprising the step of substantially purifying said protein corresponding to said variant or homologue.

33. A method for identifying an allelic variant or heterospecific homologue of a human cAMP-GEF gene comprising:

choosing an antibody capable of selectively binding to a human cAMP-GEF protein;

mixing said antibody with a sample of proteins which may contain a protein corresponding to said variant or homologue; and

detecting binding of said antibody to said protein corresponding to said variant or homologue.

34. A method as in claim 33 wherein said sample comprises a sample of proteins selected from the group consisting of human proteins, human fusion proteins, and proteolytic fragments thereof.

35. A method as in claim 33 wherein said sample comprises a sample of proteins selected from the group consisting of mammalian proteins, mammalian fusion proteins, and proteolytic fragments thereof.

36. A method as in claim 33 wherein said sample comprises a sample of proteins selected from the group consisting of invertebrate proteins, invertebrate fusion proteins, and proteolytic fragments thereof.

37. A method as in claim 33 further comprising the step of substantially purifying said protein corresponding to said variant or homologue.

38. An isolated nucleic acid comprising an allelic variant or a heterospecific homologue of a gene selected from the group consisting of a human CalDAG-GEF gene, and a human cAMP-GEF gene.

39. An isolated nucleic acid encoding an allelic variant or heterospecific homologue of a protein selected from the group consisting of a human CalDAG-GEF protein, and a human cAMP-GEF protein.

40. An isolated nucleic acid comprising a recombinant vector including a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, and a sequence complementary to any of these sequences.

41. An isolated nucleic acid as in claim 40 wherein said vector is an expression vector and said nucleotide sequence is operably joined to a regulatory region.

42. An isolated nucleic acid as in claim 41 wherein said expression vector may express said nucleotide sequence in mammalian cells.

43. An isolated nucleic acid as in claim 42 wherein said cells are selected from the group consisting of fibroblast, liver, kidney, spleen, bone marrow, and neurological cells.

44. An isolated nucleic acid as in claim 42 wherein said vector is selected from the group consisting of vaccinia virus, adenovirus, retrovirus, neurotropic viruses, and Herpes simplex.

45. An isolated nucleic acid as in claim 41 wherein said expression vector encodes at least a functional domain of a protein selected from the group consisting of normal CalDAG-GEFI, a normal CalDAG-GEFII, a mutant CalDAG-GEFI, a mutant CalDAG-GEFII, a normal cAMP-GEFI, a normal cAMP-GEFII, a mutant cAMP-GEFI, and a mutant cAMP-GEFII.

46. An isolated nucleic acid as in claim 41 wherein said vector further comprises sequences encoding an exogenous protein operably joined to said nucleotide sequence and whereby said vector encodes a fusion protein.

47. An isolated nucleic acid as in claim 46 wherein said exogenous protein is selected from the group consisting of lacZ, trpE, maltose-binding protein, poly-His tags, and glutathione-S-transferase.

48. An isolated nucleic acid comprising a recombinant expression vector including nucleotide sequences corresponding to an endogenous regulatory region of a gene selected from the group consisting of a CalDAG-GEF gene, and a cAMP-GEF gene.

49. An isolated nucleic acid as in claim 48 wherein said endogenous regulatory region is operably joined to a marker gene.

50. A host cell transformed with an expression vector of any one of claims 41-49, or a descendant thereof.

51. A host cell as in claim 50 wherein said host cell is selected from the group consisting of bacterial cells and yeast cells.

52. A host cell as in claim 50 wherein said host cell is selected from the group consisting of fetal cells, embryonic stem cells, zygotes, gametes, and germ line cells.

53. A host cell as in claim 50 wherein said cell is selected from the group consisting of fibroblast, liver, kidney, spleen, bone marrow and neurological cells.

54. A host cell as in claim 50 wherein said cell is an invertebrate cell.

55. A non-human animal model for cancer, wherein a genome of said animal, or an ancestor thereof, has been modified by at least one recombinant construct, and wherein said recombinant construct has introduced a modification selected from the group consisting of

(a) insertion of nucleotide sequences encoding at least a functional domain of a heterospecific normal CalDAG-GEF gene;

(b) insertion of nucleotide sequences encoding at least a functional domain of a heterospecific mutant CalDAG-GEF gene;

(c) insertion of nucleotide sequences encoding at least a functional domain of a conspecific homologue of a heterospecific mutant CalDAG-GEF gene;

(d) inactivation of an endogenous CalDAG-GEF gene;

(e) insertion of nucleotide sequences encoding at least a functional domain of a heterospecific normal cAMP-GEF gene;

(f) insertion of nucleotide sequences encoding at least a functional domain of a heterospecific mutant cAMP-GEF gene;

(g) insertion of nucleotide sequences encoding at least a functional domain of a conspecific homologue of a heterospecific mutant cAMP-GEF gene; and

(h) inactivation of an endogenous cAMP-GEF gene.

56. A non-human animal model as in claim 55 wherein said cancer is related to the Ras-pathway.

57. A non human animal model as in claim 56 wherein said cancer is selected from the group consisting of lung cancer, pancreatic cancer, breast cancer, colorectal cancer, and myeloid leukemia.

58. An animal model as in claim 55 wherein said modification is an insertion of a nucleotide sequence encoding at least a functional domain of a protein selected from the group consisting of a normal human CalDAG-GEF, and a normal cAMP-GEF gene.

59. An animal model as in claim 55 wherein said modification is an insertion of a nucleotide sequence encoding at least a functional domain of a protein selected from the group consisting of a mutant human CalDAG-GEF, and a mutant human cAMP-GEF gene.

60. An animal as in claim 55 wherein said animal is selected from the group consisting of rats, mice, hamsters, guinea pigs, rabbits, dogs, cats, goats, sheep, pigs, and non-human primates.

61. An animal as in claim 55 wherein said animal is an invertebrate.

62. A method for producing at least a functional domain of a protein selected from the group consisting of a CalDAG-GEF protein, and a cAMP-GEF protein, said method comprising culturing a host cell of any of claims 50-54 under suitable conditions to produce said protein by expressing said nucleic acid.

63. A substantially pure preparation of a protein selected from the group consisting of a normal CalDAG-GEF protein, a mutant CalDAG-GEF protein, a normal cAMP-GEF protein, and a mutant cAMP-GEF protein.

64. A substantially pure preparation as in claim 63 wherein said protein comprises a normal protein selected from the group consisting of

(a) a protein comprising the amino acid sequence of SEQ ID NO: 2;

(b) a protein comprising the amino acid sequence of SEQ ID NO: 4;

(c) a protein comprising the amino acid sequence of SEQ ID NO: 6;

(d) a protein comprising the amino acid sequence of SEQ ID NO: 8;

(e) a protein comprising the amino acid sequence of SEQ ID NO: 10;

(f) a protein comprising the amino acid sequence of SEQ ID NO: 12;

(g) a protein comprising the amino acid sequence of SEQ ID NO: 14;

(h) a protein comprising the amino acid sequence of SEQ ID NO: 16; and

(i) a protein comprising the amino acid sequence of SEQ ID NO: 18.

65. A substantially pure preparation of a polypeptide comprising an amino acid sequence of at least 4 consecutive amino acid residues selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, and SEQ ID NO: 18.

66. A substantially pure preparation of a polypeptide comprising an amino acid sequence of at least 10 consecutive amino acid residues selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, and SEQ ID NO: 18.

67. A substantially pure preparation of a polypeptide comprising an amino acid sequence of at least 15 consecutive amino acid residues selected from the group consisting of SEQ ID NO:

2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, and SEQ ID NO: 18.

68. A substantially pure preparation of a polypeptide comprising at least one functional domain of a protein selected from the group consisting of a normal CalDAG-GEF protein, a mutant CalDAG-GEF protein, a normal cAMP-GEF protein, and a mutant cAMP-GEF protein.

69. A substantially pure preparation of a polypeptide comprising an antigenic determinant of a protein selected from the group consisting of a normal CalDAG-GEF protein, a mutant CalDAG-GEF protein, a normal cAMP-GEF protein, and a mutant cAMP-GEF protein.

70. A method of producing antibodies which selectively bind to a CalDAG-GEF protein comprising the steps of

administering an immunogenically effective amount of a CalDAG-GEF immunogen to an animal;

allowing said animal to produce antibodies to said immunogen; and

obtaining said antibodies from said animal or from a cell culture derived therefrom.

71. A method of producing antibodies which selectively bind to a cAMP-GEF protein comprising the steps of

administering an immunogenically effective amount of a cAMP-GEF immunogen to an animal;

allowing said animal to produce antibodies to said immunogen; and

obtaining said antibodies from said animal or from a cell culture derived therefrom.

72. A substantially pure preparation of an antibody which selectively binds to an antigenic determinant of a protein selected from the group consisting of a normal CalDAG-GEF protein, a mutant CalDAG-GEF protein, a normal cAMP-GEF protein, and a mutant cAMP-GEF protein.

73. A substantially pure preparation of an antibody as in claim 72 wherein said antibody selectively binds to an antigenic determinant of a mutant CalDAG-GEF and fails to bind to a normal CalDAG-GEF protein.

74. A substantially pure preparation of an antibody as in claim 72 wherein said antibody selectively binds to an antigenic determinant of a mutant cAMP-GEF and fails to bind to a normal cAMP-GEF protein.

75. A cell line producing an antibody of any one of claims 72-74.

76. A method for identifying compounds which can modulate the expression of a CalDAG-GEF gene comprising:

contacting a cell with a test candidate wherein said cell includes a regulatory region of a CalDAG-GEF gene operably joined to a coding region; and

detecting a change in expression of said coding region.

77. A method for identifying compounds which can modulate the expression of a cAMP-GEF gene comprising:

contacting a cell with a test candidate wherein said cell includes a regulatory region of a cAMP-GEF gene operably joined to a coding region; and

detecting a change in expression of said coding region.

78. A method as in claim 76 or 77 wherein said change comprises a change in a level of an mRNA transcript encoded by said coding region.

79. A method as in claim 78 wherein said change comprises a change in a level of a protein encoded by said coding region.

80. A method as in claim 78 wherein said change is a result of an activity of a protein encoded by said coding region.

81. A method as in claim 78 wherein said coding region encodes a marker protein selected from the group consisting of β-galactosidase, alkaline phosphatase, green fluorescent protein, and luciferase.

82. A method for identifying compounds which can selectively bind to a CalDAG-GEF protein comprising the steps of

providing a preparation including at least one CalDAG-GEF component;

contacting said preparation with a sample including at least one candidate compound; and

detecting binding of said CalDAG-GEF component to said candidate compound.

83. A method for identifying compounds which can selectively bind to a cAMP-GEF protein comprising the steps of

providing a preparation including at least one cAMP-GEF component;

contacting said preparation with a sample including at least one candidate compound; and

detecting binding of said cAMP-GEF component to said candidate compound.

84. The method in claim 82 wherein said binding to said CalDAG-GEF component is detected by an assay selected from the group consisting of: affinity chromatography, co-immunoprecipitation, a Biomolecular Interaction Assay, and a yeast two-hybrid system.

85. The method in claim 83 wherein said binding to said cAMP-GEF component is detected by an assay selected from the group consisting of: affinity chromatography, co-immunoprecipitation, a Biomolecular Interaction Assay, and a yeast two-hybrid system.

86. A method of identifying compounds which can modulate activity of a CalDAG-GEF comprising the steps of

providing a cell expressing a normal or mutant CalDAG-GEF gene;

contacting said cell with at least one candidate compound; and

detecting a change in a marker of said activity.

87. A method of identifying compounds which can modulate activity of a cAMP-GEF comprising the steps of

providing a cell expressing a normal or mutant cAMP-GEF gene;

contacting said cell with at least one candidate compound; and

detecting a change in a marker of said activity.

88. A method as in claim 86 wherein measurement of said marker indicates a difference between cells bearing an expressed mutant CalDAG-GEF gene and otherwise identical cells free of an expressed mutant CalDAG-GEF gene.

89. A method as in claim 86 wherein said change comprises a change in a non-specific marker of cell physiology selected from the group consisting of pH, intracellular calcium, cyclic AMP levels, GTP/GDP ratios, phosphatidylinositol activity, and protein phosphorylation.

90. A method as in claim 86 wherein said change comprises a change in expression of said CalDAG-GEF.

91. A method as in claim 86 wherein said change comprises a change in occurrence or rate of apoptosis or cell death.

92. A method as in claim 86 wherein said cell is a cell cultured *in vitro*.

93. A method as in claim 92 wherein said cell is a transformed host cell of any one of claims 50-54.

94. A method as in claim 92 wherein said cell is explanted from a host bearing at least one mutant CalDAG-GEF gene.

95. A method as in claim 92 wherein said cell is explanted from a transgenic animal of any one of claims 55-61.

96. A method as in claim 86 wherein said cell is a cell in a live animal.

97. A method as in claim 96 wherein said cell is a cell of a transgenic animal of any one of claims 55-61.

98. A method as in claim 86 wherein said cell is in a human subject in a clinical trial.

99. A method as in claim 87 wherein measurement of said marker indicates a difference between cells bearing an expressed mutant cAMP-GEF gene and otherwise identical cells free of an expressed mutant cAMP-GEF gene.

100. A method as in claim 87 wherein said change comprises a change in a non-specific marker of cell physiology selected from the group consisting of pH, intracellular calcium, cyclic AMP levels, GTP/GDP ratios, phosphatidylinositol activity, and protein phosphorylation.

101. A method as in claim 87 wherein said change comprises a change in expression of said cAMP-GEF.

102. A method as in claim 87 wherein said change comprises a change in occurrence or rate of apoptosis or cell death.

103. A method as in claim 87 wherein said cell is a cell cultured *in vitro*.

104. A method as in claim 103 wherein said cell is a transformed host cell of any one of claims 50-54.

105. A method as in claim 103 wherein said cell is explanted from a host bearing at least one mutant cAMP-GEF gene.

106. A method as in claim 103 wherein said cell is explanted from a transgenic animal of any one of claims 55-61.

107. A method as in claim 87 wherein said cell is a cell in a live animal.

108. A method as in claim 107 wherein said cell is a cell of a transgenic animal of any one of claims 55-61.

109. A method as in claim 87 wherein said cell is in a human subject in a clinical trial.

110. A diagnostic method for determining if a subject bears a mutant CalDAG-GEF gene comprising the steps of

providing a biological sample of said subject; and

detecting in said sample a mutant CalDAG-GEF nucleic acid, a mutant CalDAG-GEF protein, or a mutant CalDAG-GEF activity.

111. A method as in claim 111, wherein a mutant CalDAG-GEF nucleic acid is detected by an assay selected from the group consisting of direct nucleotide sequencing, probe specific hybridization, restriction enzyme digest and mapping, PCR mapping, ligase-mediated PCR

detection, RNase protection, electrophoretic mobility shift detection, and chemical mismatch cleavage.

112. A method as in claim 110, wherein a mutant CalDAG-GEF protein is detected by an assay selected from the group consisting of an immunoassay, a protease assay, and an electrophoretic mobility assay.

113. A diagnostic method for determining if a subject bears a mutant cAMP-GEF gene comprising the steps of

providing a biological sample of said subject; and

detecting in said sample a mutant cAMP-GEF nucleic acid, a mutant cAMP-GEF protein, or a mutant cAMP-GEF activity.

114. A method as in claim 113, wherein a mutant cAMP-GEF nucleic acid is detected by an assay selected from the group consisting of direct nucleotide sequencing, probe specific hybridization, restriction enzyme digest and mapping, PCR mapping, ligase-mediated PCR detection, RNase protection, electrophoretic mobility shift detection, and chemical mismatch cleavage.

115. A method as in claim 113, wherein a mutant cAMP-GEF protein is detected by an assay selected from the group consisting of an immunoassay, a protease assay, and an electrophoretic mobility assay.

116. A pharmaceutical preparation comprising a substantially pure CalDAG-GEF protein and a pharmaceutically acceptable carrier.

117. A pharmaceutical preparation comprising a substantially pure cAMP-GEF protein and a pharmaceutically acceptable carrier.

118. A pharmaceutical preparation comprising an expression vector operably encoding a protein selected from the group consisting of a CalDAG-GEF protein, and a cAMP-GEF protein, wherein said expression vector may express said CalDAG-GEF protein or said cAMP-GEF protein in a human subject, and a pharmaceutically acceptable carrier.

119. A pharmaceutical preparation comprising an expression vector operably encoding a CalDAG-GEF antisense sequence, wherein said expression vector may express said CalDAG-GEF antisense sequence in a human subject, and a pharmaceutically acceptable carrier.

120. A pharmaceutical preparation comprising an expression vector operably encoding a cAMP-GEF antisense sequence, wherein said expression vector may express said cAMP-GEF antisense sequence in a human subject, and a pharmaceutically acceptable carrier.

121. A pharmaceutical preparation comprising a substantially pure antibody, and a pharmaceutically acceptable carrier,

wherein said antibody selectively binds to a mutant protein selected from the group consisting of a mutant CalDAG-GEF protein, and a mutant cAMP-GEF protein.

122. A pharmaceutical preparation as in claim 121 wherein said preparation is essentially free of an antibody which selectively binds a normal CalDAG-GEF protein.

123. A pharmaceutical preparation as in claim 121 wherein said preparation is essentially free of an antibody which selectively binds a normal cAMP-GEF protein.

124. A pharmaceutical preparation comprising a substantially pure preparation of an antigenic determinant of a mutant CalDAG-GEF protein or a mutant cAMP-GEF protein.

125. A pharmaceutical preparation as in claim 124 wherein said preparation is essentially free of an antigenic determinant of a normal CalDAG-GEF protein.

126. A pharmaceutical preparation as in claim 124 wherein said preparation is essentially free of an antigenic determinant of a normal cAMP-GEF protein.

127. A method for identifying compounds according to claim 83, wherein the cAMP-GEF component is a cAMP-GEF domain selected from the group consisting of SCR1, SCR2, SCR3, and cAMP-binding domain.

128. A method for identifying compounds according to claim 82, wherein the CalDAG-GEF component is a CalDAG-GEF domain selected from the group consisting of SCR1, SCR2, SCR3, DAG-binding and an EF hand domain.

129. A substantially pure preparation of a polypeptide comprising a domain selected from the group consisting of a CalDAG-GEF SCR1 domain, a CalDAG-GEF SCR2 domain, CalDAG-GEF SCR3 domain, CalDAG-GEF DAG-binding domain, CalDAG-GEF EF hand domain.

130. A substantially pure preparation of a polypeptide comprising a domain selected from the group consisting of a cAMP-GEF SCR1 domain, a cAMP-GEF SCR2 domain, cAMP-GEF SCR3 domain, cAMP-GEF cAMP-binding domain.